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IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

In re application of
Yasushi OCHIAI et al.
Application No.: 10/091,559 Art Unit: 1615
Filed: March 7, 2002 Examiner: RACHEL M. BENNET

For: **METHOD OF MANUFACTURING DRUG GRANULES, THE DRUG GRANULES AND PHARMACEUTICAL PREPARATION CONTAINING THE DRUG GRANULES**

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Declaration Under 37 CFR § 1.132

Sir:

In connection with the above-identified U.S. patent application, I, Yasushi Ochiai, a citizen of Japan and residing at 203, 5-3-15, Furuedai, Suita-Shi, Osaka, 565-0874, Japan, say and declare as follows:

1. I received a Master's degree from the Department of Polymer Chemistry of the Faculty of Engineering, Kyoto University in Japan in 1992.

2. I have been working at Sumitomo Pharmaceuticals Research Center since 1992. I have been studying controlled release oral formulations or preparations.

3. I am a co-author of the paper of the list attached.

4. I am one of the inventors in U.S. Serial Number 10/091,559 and I am very familiar with the subject matter thereof and have been researching the subject matter thereof since 2001.

5. Materials

All raw materials were commercially available in Japan.

Lysine hydrochloride: L-Lysine monohydrochloride (Kyowa Hakko Kogyo Co. Ltd.)

Methacrylic acid copolymer LD: Polyquid PA-30S (Sanyo Chemical Industries Ltd.)

Sucrose Esters of Fatty Acids: DK ester F-50P (Dai-ichi Seiyaku Co. Ltd.)

Macrogol 6000: PEG6000P (Sanyo Chemical Industries Ltd.)

6. Experiment

6.1. Layering (Granulation)

Lysine hydrochloride granule of the present invention was prepared by the method described in the present patent specification.

600g of lysine hydrochloride were charged in the Rotary fluidized bed granulator MP-01 at the first process of granulation. Fluidization was set in motion and the layering solution was sprayed. The layering operation was carried out under the following conditions:

Equipment used: Rotary fluidized bed granulator: Multiplex MP-01 (Powrex Corporation)

Conditions of first granulation:	
Lysine hydrochloride charge	600g
Air flow	$40m^3/h$
Air inlet temperature	80 degrees Celsius
Spray nozzle position	Top
Spray air pressure	1.1bar
Rate of spraying solution	5～11g/min
Rotation rate of the rotor plate	100～200r.p.m.
Layering solution	
Lysine hydrochloride	600g
Purified water	900g
Solution temperature	Room temperature

On and after the second granulation, 800g of layered lysine granule were charged in the MP-01. The layering operation was carried out under the following conditions:

Conditions of second to fourth granulation:	
Layered granule charge	800g
Air flow	40～50m^3/h
Air inlet temperature	80 degrees Celsius
Spray Nozzle position	Tangential
Spray air pressure	0.8～1.1bar
Rate of spraying solution	6～12g/min
Rotation rate of the rotor plate	200～300r.p.m.
Layering solution	
Lysine hydrochloride	400g
Purified water	600g
Solution temperature	Room temperature

Conditions of fifth to eighth granulation:	
Layered granule charge	800g
Air flow	50～55m^3/h
Air inlet temperature	80 degrees Celsius
Spray nozzle position	Tangential
Spray air pressure	0.7～1.5bar
Rate of spraying solution	6～12g/min
Rotation rate of the rotor plate	200～350r.p.m.
Layering solution	
Lysine hydrochloride	600g*
Purified water	900g*
Solution temperature	Room temperature

*Seventh Granulation	Lysine hydrochloride	800g
	Purified water	1200g

All the layered wet granules were dried by Rotary fluidized bed granulator for 5 minutes at the inlet air temperature of 80 degrees Celsius.

6.2. Coating

Granules of present invention

600g of the layered lysine granule with a diameter of between 0.59 and 0.84mm were introduced into Multiplex MP-01. The coating operation was carried out under the following conditions similar to the method of US 5,300,318. The granules were coated up

to about 60% by enteric coating agent Polyquid PA-30S and sampled every 10% coating.

Equipment used : Multiplex MP-01 Wurster type (Powrex Corporation)

Coating conditions:	
Layering granule (build 8th) charge	600g
Air flow	60m^3/h
Air inlet temperature	70 degrees Celsius
Spraying pressure	3.0bar
Rate of spraying solution	15g/min
Coating solution	
Polyquid PA30S	1200g (solid:360g)
DKester F-50P	20g
PEG6000P	20g
Purified water	1160g
Coating solution temperature	Room temperature

The coated wet granules were dried by Rotary fluidized bed granulator for 60 minutes at inlet air temperature of 75 degrees Celsius.

Granules of Pierre et al. (US 5,300,318)

The granules coated from 10% to 30% were used samples prepared in my first declaration (which was filed in the USPTO with the prior response of November 18, 2003). 60% coating granules were obtained by coating 40% coated granules in my first declaration (which was filed in the USPTO with the prior response of November 18, 2003).

Equipment used

Multiplex MP-01 Wurster type (Powrex Corporation)

Coating conditions:	
40% coating granule charge	390g
Air flow	$60m^3/h$
Air inlet temperature	70 degrees Celsius
Spraying pressure	3.0bar
Rate of spraying solution	12.6g/min
Coating solution	
Polyquid PA30S	540g (solid:162g)
DKester F-50P	9g
PEG6000P	9g
Purified water	522g
Coating solution temperature	Room temperature

The coated wet granules were dried by Rotary fluidized bed granulator for 60 minutes at the inlet air temperature of 75 degrees Celsius.

6.3. Measurement of granular strength

The granular strength was measured using a table-top material tester (EZ Test-20N, Shimadzu Corporation) as described in Evaluation test 3 of the specification. One lysine granule of present invention obtained by eighth granules and the granule of Pierre et al. were placed on a sample table of the table-top material tester. Using an upper compression jig having a diameter of 5mm, the granules were compressed in a compression mode at 0.5mm/min and the maximum peak was taken as the strength. The measurement was repeated 3 times and the measures were averaged. The granular strength is the strength divided by the sectional area.

6.4. SEM (Scanning Electron Microscope)

The image of SEM was obtained by the below conditions.

<SEM conditions>

Machine: Scanning Electron Microscope S−530 (Hitachi High-Technologies)

Ion sputter E−1030 (Hitachi High-Technologies)

Thickness of vacuum evaporation: 15nm

Sample: Layered lysine granule and coated lysine granule with Polyquid PA30S of the present invention,

Other images of SEM were quoted from my first declaration (which was filed in the USPTO with the prior response of November 18, 2003).

6.5. Dissolution test

The dissolution of lysine from coated granule obtained in the above mentioned procedures and from my first declaration was evaluated according to Japan pharmacopoeia, method 2 (Paddle Method) of dissolution test.

<Analysis conditions>

Dissolution tester NTR-6100A (Toyama Sangyo Co., Ltd.)
Test dissolution: pH1.2
Amount of solution: 900ml
Temperature of solution: 37 degrees Celsius
Rate of rotation: 100rev/min
Sampling amount: 5ml
Measurement method: absorption at 210 nm of sample solution was measured by UV-Visible Spectrophotometer UV-1600 (Shimadzu Corporation).

7. Results

7.1. Granular strength

Table 1 is a result of the measurement of the lysine granule of the present invention.

Table 1 Granular Strength of Lysine Granule

	(gf/mm^2)
Layered lysine granule of the present invention	1150
Non-polished granule (US 5,300,318)	304
20% polishing granule (US 5,300,318)	453

The granule of the present invention has a much larger strength than that of granules of US 5,300,318.

7.2. SEM

Fig. 1 Surface of Granule of The Present Invention

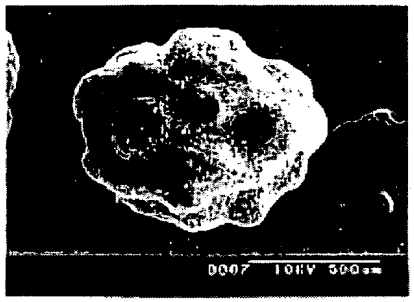


Fig. 2 Magnification of Fig. 1

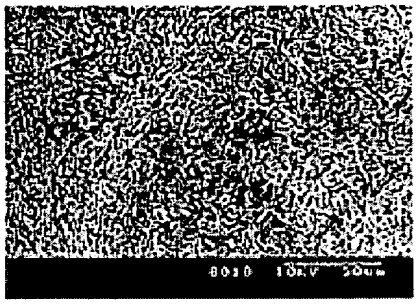


Fig. 3 Cross-section of Granule of The Present Invention

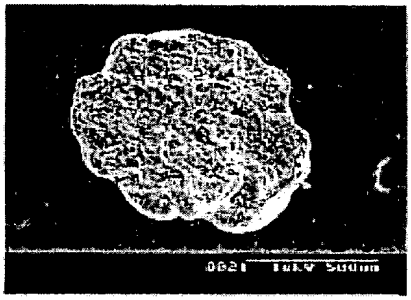


Fig. 4 Magnification of Fig. 3

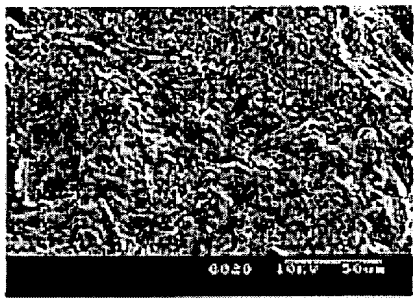


Fig. 5 - Surface of 60% Coated Granules of The Present Invention

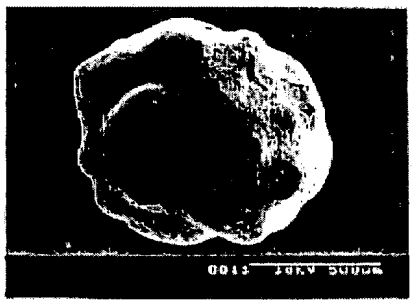


Fig. 6 - Cross-section of Fig. 5

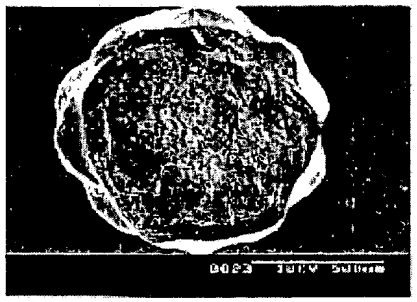


Fig. 7 Surface of Non-polished Granule of Pierre at al.

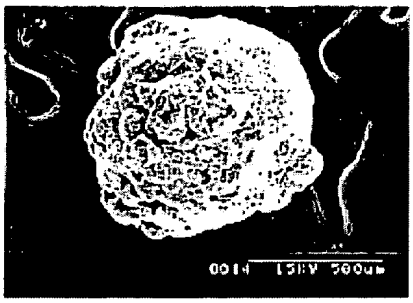


Fig. 8 Magnification of Fig. 7

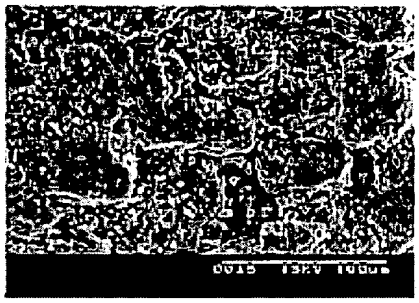


Fig. 9 Cross-section of Non-polished Granule of Pierre et al.

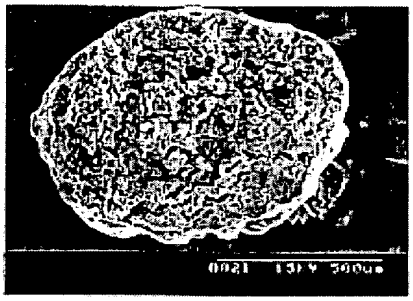


Fig. 10 Magnification of Fig. 9

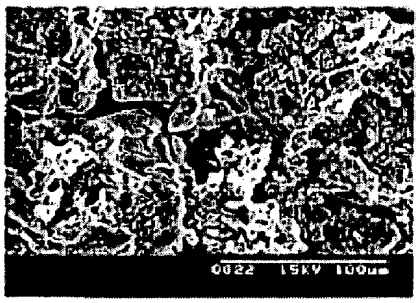


Fig. 11 Surface of 20% Polished Granule of Pierre et al.

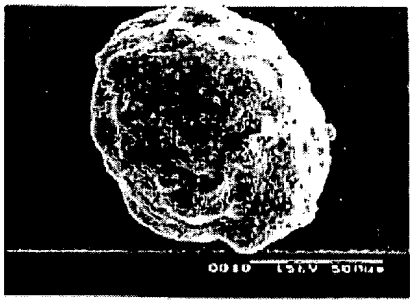


Fig. 12 Magnification of Fig. 11

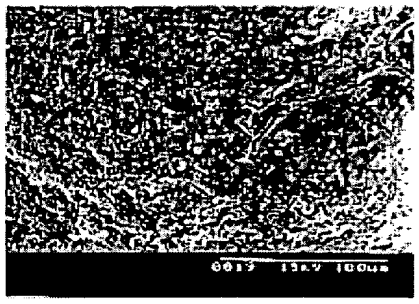


Fig. 13 Cross-section of 20% Polished Granule of Pierre et al.

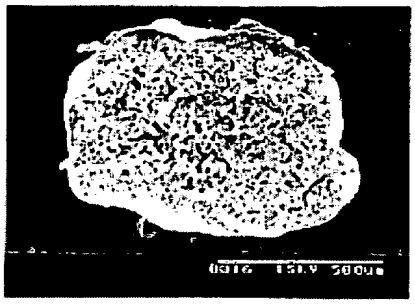


Fig. 14 - Magnification of Fig. 13

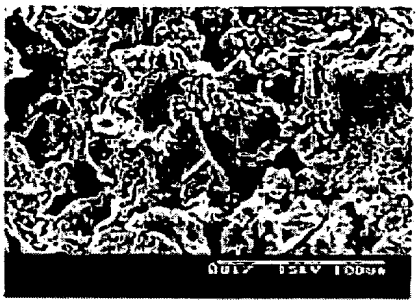


Fig. 15 - Surface of 60% Coated Granule of Pierre et al.

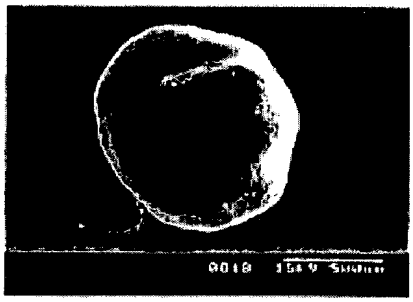
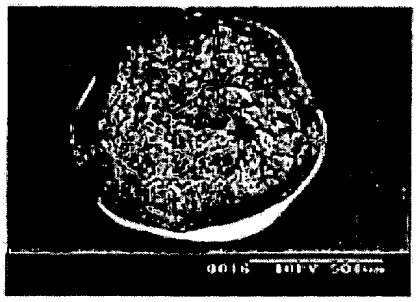


Fig. 16 – Cross-section of Fig. 15



Figures 1-4 show that the granules of the present invention have homogeneous structure.

Figures 7-10 show that the granules of Pierre et al. (US 5,300,318) have porous and non-homogeneous structure.

Figures 11-14 show the lysine granules of Pierre et al. after polishing have smooth surfaces, but the inner part of the polished granules still has porous and non-homogeneous structure.

Figure 5 shows that the granules of the present invention have smooth and homogeneous surfaces.

Figure 15 shows that coated granules of Pierre et al. having smooth and homogeneous surfaces.

Figures 6 and 16 show that coated granule of the present invention and Pierre et al. have almost same thickness of coating agent.

7.3. Dissolution test

Figure 17 is a graph showing the results of the dissolution test of the coated lysine granules of the present invention.

Figure 18 is a graph showing the results of the dissolution test of the coated lysine granules of Pierre et al.

Figure 17

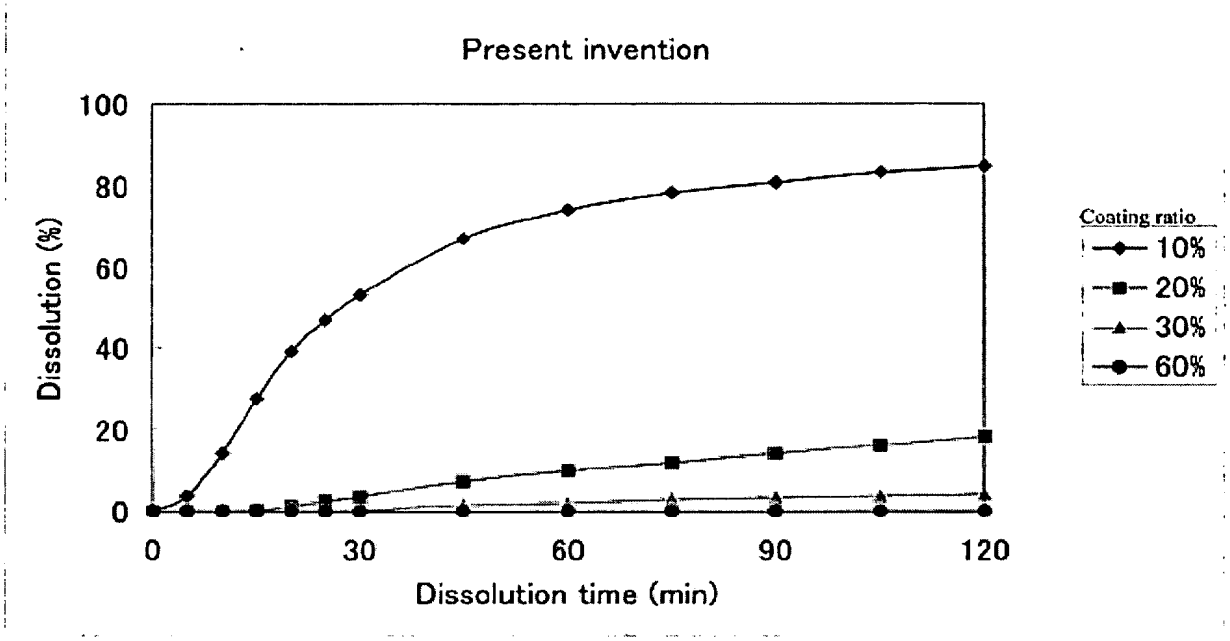
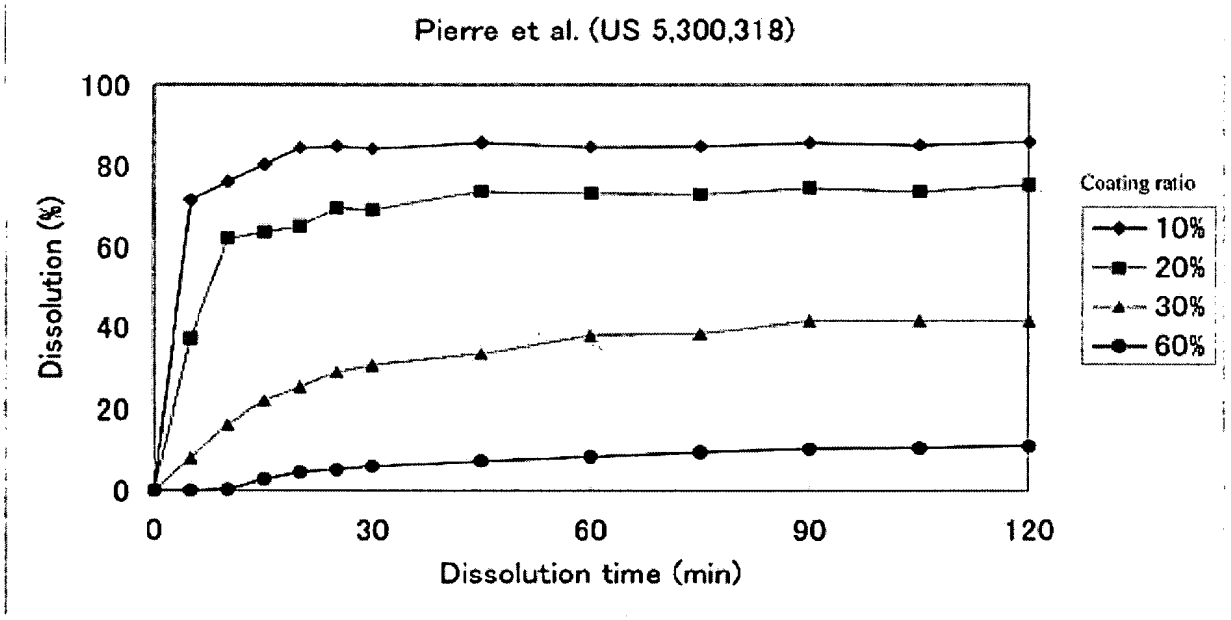


Figure 18



Coated granules of present invention show an excellent ability as an enteric preparation for human use, as shown in Fig. 17. It is desirable for an enteric preparation that dissolution rate of 1 to 2 hours is less than 5 % to the solution of pH 1.2 . 30 % of coating ratio is sufficient for the granules of the present invention.

Even a 60% Coated granules of Pierre et al. do not show enough resistant ability to the solution of pH 1.2, as shown in Fig. 18.

8. Conclusion

The test results provided above show that the resistant ability to the solution of pH 1.2 of the present invention is quite distinct and different from that of Pierre et al. (US 5,300,318). The difference of the results is considered to be from the property of granules between the present invention and Pierre et al. During the coating process the strength of granules of Pierre at al. is not strong enough. It is considered that the granules of Pierre at al. are worn away during the coating process and small particles of active ingredient are produced. The small particles is considered to exist in and on the enteric coated layer of the granules of Pierre at al. and to dissolute into the solution.

I believe that those result and difference between the granule of the present invention and the granules of Pierre at al. is unexpected and that the present invention is not obvious from Pierre et al. for the man skilled in the art.

9. The undersigned declares further that all statement made herein of his own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that Such willful false statement may jeopardize the validity of above identified application or any patent issuing thereon.

June 23, 2004

Yasushi Ochiai

Yasushi Ochiai

List of Publication

1) pH-sensitive gating by conformational change of polypeptide brush grafted on porous polymer membrane, Ito Y., Ochiai Y., Park YS. and Imanishi Y., J. Am. Chem. Soc. 119, 1619-23, 1997